

61803



PATENT 600-1-087 CIP21

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

APPLICANT(S): FRIEDMAN ET AL.

SERIAL NO.: 08/485,943

DATE FILED: JUNE 7, 1995

EXAMINER: G. DRAPER

ART UNIT: 1803 1815

FOR: MODULATORS OF BODY WEIGHT, CORRESPONDING  
NUCLEIC ACIDS AND PROTEINS, AND DIAGNOSTIC AND  
THERAPEUTIC USES THEREOF

RALEY 12  
88

**CERTIFICATE OF MAILING UNDER 37 CFR § 1.8**

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, DC 20231 on June 16, 1997

David A. Jackson (Registration No. 26,742)

(Name of Registered Representative)

(Signature and Date)

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

**INFORMATION DISCLOSURE STATEMENT**

In accordance with Applicant's and Applicant's representatives' Duty of Disclosure under 37 CFR § 1.56, and pursuant to 37 CFR § 1.97 and MPEP 717.05(b), Applicant submits herewith documentary information for consideration by the Examiner. Information herein cited is only set forth in fulfillment of Applicant's duty of candor in disclosing all information brought to his attention, and is not an admission that it can be used adversely. The publications forwarded herewith are listed on the enclosed Form PTO-1449. Applicant requests that the Examiner, upon reviewing the enclosed materials, initial the enclosed form and return a copy thereof in accordance with the instructions on the form.

Since all the publications (AA through HO) listed on the attached Form PTO-1449 were already supplied with an Information Disclosure Statement in connection with Application U.S. Serial No. 08/292,345, filed on August 17, 1994, pursuant to 37 CFR § 1.98(d) copies of the cited references are hereby not enclosed.

For the convenience of the Examiner, the applicants have broken down the listed references into twelve groups with respect to the subject matter of the references. The groups include,

- I.Mapping and Cloning of Obesity Associated Genes
- II.Obesity-Associated Proteins, Genes, Mutants and their Regulation
- III.Ob Encoded Proteins, Fragments Thereof, and Their Biological Effects
- IV.Biology, Physiology and Genetics of Obesity and Weight Regulation
- V.Gene Mapping (General)
- VI.Pharmaceutical and Pharmacological Methods and Materials, Drug Delivery
- VII.Molecular Biological and Recombinant Methods and Therapies
- VIII.Modification of Proteins
- IX.Immunological Materials and Methods
- X.Analytical Methods
- XI.Synthetic Methods
- XII.Receptors/Ligands
- XIII.Miscellaneous

The references are set out in alphabetical order in each section.

**I. Mapping and Cloning of Obesity Associated Genes**

EP 0 566 410 A2      10/20/93  
Their Preparation and Their Use"

EPO "Derivatives of Adipogenesis Inhibitory Factor,

Bahary et al., "Microdissection and Microcloning of Mid-Chromosome 4: Genetic Mapping of 41 Microdissection Clones," *Genomics*, 16:113-122 (1993).

Bahary et al., "Microdissection of proximal mouse Chromosome 6: identification of RFLPs tightly linked to the ob mutation," *Mammalian Genome*, 4(9):511-515 (1993).

Bahary et al., "Molecular mapping of the mouse db mutation," *Proc. Nat. Acad. Sci. USA*, 87:8642-8646 (November 1990).

Bahary et al., "Molecular Mapping of Mouse Chromosomes 4 and 6: Use of a Flow-Sorted Robertsonian Chromosome," *Genomics*, 13:761-769 (1992).

Blank et al., "Mouse Chromosome 4," *Mammalian Genome*, 1:S51-S78 (1991).

Coleman, "Obese and Diabetes: Two Mutant Genes Causing Diabetes-Obesity Syndromes in Mice," *Diabetologia*, 14:141-148 (1978).

Friedman et al., "Genet. Anal. of Comp. Disorders," *Ann. NY Acad. Sci.* 630:100-15 (1991).

Friedman et al., "Molecular mapping of obesity genes," *Mam. Genome*, 1:130-44 (1991).

Friedman et al., "Tackling a Weighty Problem," *Cell*, 69:217-220 (April 17, 1992).

Froguel and Hagar, "Human diabetes and obesity: tracking down the genes," *TIBTECH*, 13:52-55 (February 1995).

Funahashi et al., "Enhanced Expression of Rat Obese (ob) Gene in Adipose Tissues of Ventromedial Hypothalamus (VMH)-Lesioned Rats," *Biochem. Biophys. Res. Comm.*, 211(2):469-475 (June 15, 1995).

Geffroy et al., "Localization of the Human OB Gene (OBS) to Chromosome 7q32 by Fluorescence in Situ Hybridization," *Genomics*, 28:603-604 (1995).

Green et al., "A Human Chromosome 7 Yeast Artificial Chromosome (YAC) Resource: Construction, Characterization, and Screening," *Genomics*, 25:170-183 (1995).

Green et al., "Integration of physical, genetic and cytogenetic maps of human chromosome 7: isolation and analysis of yeast artificial chromosome clones for 117 mapped genetic markers," *Hum. Mol. Genet.*, 3(3):489-501 (1994).

Green et al., "Systematic Generation of Sequence-Tagged Sites for Physical Mapping of Human Chromosomes: Application to the Mapping of Human Chromosome 7 Using Yeast Artificial Chromosomes," *Genomics*, 11:548-564 (1991).

Green et al., "The Human Obese (OB) Gene: RNA Expression Pattern and Mapping on the Physical, Cytogenetic, and Genetic Maps of Chromosome 7," *Genome Res.*, 5:5-12 (1995).

Murakami et al., "Cloning of Rat OBESE DNA and Its Expression in Obese Rats," *Biochem. Biophys. Res. Comm.*, 209:944-952 (1995).

Ogawa et al., "Molecular Cloning of Rat Obese cDNA and Augmented Gene Expression in Genetically Obese Zucker Fatty (fa/fa) Rats," *J. Clin. Invest.*, 96:1647-1652 (1995).

Truett et al., "Rat obesity gene fatty (fa) maps to chromosome 5: Evidence for homology with the mouse gene diabetes (db)," *Proc. Natl. Acad. Sci. USA*, 88:7806-7809 (September 1991).

Weigle, "Identification of Candidate Genes for a Factor Regulating Energy Balance in Humans," *Pennington Cent. Nutr. Ser.*, 2:22-36 (1992).

Zhang et al., "Positional cloning of the mouse obese gene and its human homologue," *Nature*, 372:425-432 (December 1, 1994) and its errata "Positional cloning of the mouse obese gene

and its human homologue," *Nature*, 374:479 (March 30, 1995).

## **II. Obesity-Associated Proteins, Genes, Mutants and their Regulation**

Becker et al., "Diet- and Diabetes-induced changes of ob gene expression in rat adipose tissue," *FEBS Lett.*, 371:324-328 (1995).

Campfield et al., "Recombinant Mouse OB Protein: Evidence for a Peripheral Signal Linking Adiposity and Central Neural Networks", *Science*, 279:546-549 (July 28, 1995).

Considine et al., "Evidence Against Either a Premature Stop Codon or the Absence of Obese Gene mRNA in Human Obesity," *J. Clin. Invest.*, 95:2986-2988 (June 1995).

De Vos et al., "Induction of ob Gene Expression by Corticosteroids Is Accompanied by Body Weight Loss and Reduced Food Intake," *J. Biol. Chem.*, 270(27):15958-15961 (1995).

Frederich et al., "Expression of ob mRNA and its Encoded Protein in Rodents," *J. Clin. Invest.*, 96:1658-1663 (September 1995).

Friedman et al., "Tackling a Weighty Problem," *Cell*, 69:217-220 (April 17, 1992).

Green et al., "The Human Obese (OB) Gene:RNA Expression Pattern and Mapping on the Physical, Cytogenetic, and Genetic Maps of Chromosome 7," *Genome Res.*, 5:5-12 (1995).

Halaas et al., "Weight-Reducing Effects of the Plasma Protein Encoded by the obese Gene", *Science*, 269:543-546 (July 28, 1995).

Lonnqvist et al., "Overexpression of the obese (ob) gene in adipose tissue of human obese subjects," *Nature Med.*, 1(9):950-952 (September 1995).

MacDougald et al., "Regulated expression of the obese gene product (leptin) in white adipose tissue and 3T3-L1 adipocytes," *Proc. Natl. Acad. Sci USA*, 92:9034-9037 (September 1995).

Maffei et al., "Increased expression in adipocytes of ob RNA in mice with lesions of the hypothalamus and with mutations at the db locus," *Proc. Natl. Acad. Sci. USA*, 92:6957-6960 (July 1995).

Maffei et al., "Leptin levels in human and rodent: Measurement of plasma leptin and ob RNA in obese and weight-reduced subjects," *Nature Med.*, 1(11):1155-1161 (November 1995).

Masuzaki et al., "Human Obese Gene Expression," *Diabetes*, 44:855-858 (July 1995).

Murakami et al., "Dexamethasone Regulates Obese Expression in Isolated Rat Adipocytes," *Biochem. Biophys. Res. Comm.*, 214(3):1260-1267 (September 25, 1995).

Pelleymounter et al., "Effects of the obese Gene Product on Body Weight Regulation in ob/ob Mice", *Science*, 269:540-543 (July 28, 1995).

Rentsch et al., "Recombinant OB-Gene Product Reduces Food Intake in Fasted Mice," *Biochem. Biophys. Res. Comm.*, 214(1):131-136 (September 5, 1995).

Trayhurn et al., "Acute cold-induced suppression of ob gene expression in white adipose tissue of mice: mediation by the sympathetic system," *Biochem J.*, 311:729-733 (1995).

Trayhurn et al., "Effects of fasting and refeeding on ob gene expression in white adipose tissue of lean and obese (ob/ob) mice," *FEBS Lett.*, 368:488-490 (1995).

## **III. Ob Encoded Proteins, Fragments Thereof, and Their Biological Effects**

U.S. Patent No. 5,532,336 issued July 2, 1996; DiMarchi et al., "Anti-Obesity Proteins"

U.S. Patent No. 5,521,283 issued May 28, 1996; DiMarchi et al., "Anti-Obesity Proteins"

U.S. Patent No. 5,552,524 issued September 3, 1996; Basinski et al., "Anti-Obesity Proteins"

U.S. Patent No. 5,552,523 issued September 3, 1996; Basinski et al., "Anti-Obesity Proteins"

U.S. Patent No. 5,552,522 issued September 3, 1996; DiMarchi et al., "Anti-Obesity Proteins"

Halaas et al., "Weight-Reducing Effects of the Plasma Protein Encoded by the obese Gene", *Science*, 269:543-546 (July 28, 1995).

Campfield et al., "Recombinant Mouse OB Protein: Evidence for a Peripheral Signal Linking Adiposity and Central Neural Networks", *Science*, 269:546-549 (July 28, 1995).

#### **IV. Biology, Physiology and Genetics of Obesity and Weight Regulation**

Ashwell et al., "Adipose tissue: contributions of nature and nurture to the obesity of an obese mutant mouse (ob/ob) *Proc. R. Soc. Lond.*, 195:343-353 (1977).

Bogardus et al., "Familial Dependence of the Resting Metabolic Rate," *N. Engl. J. Med.*, 315:96-100 (July 10, 1986).

Bogardus et al., "Increased Resting Metabolic Rates in Obese Subjects with Non-insulin-dependent Diabetes Mellitus and the Effect of Sulfonylurea Therapy," *Diabetes*, 35:1-5 (1986).

Bray, "1989 McCollum Award Lecture. Genetic and hypothalamic mechanisms for obesity-finding the needle in the haystack," *Am. J. Clin. Nutr.*, 50:891-902 (1989).

Coleman, "Effects of Parabiosis of Obese with Diabetes and Normal Mice," *Diabetologia*, 9:294-298 (1973).

Coleman, "Obese and Diabetes: Two Mutant Genes Causing Diabetes-Obesity Syndromes in Mice," *Diabetologia*, 14:141-148 (1978).

Dani et al., "Molecular biology techniques in the study of adipocyte differentiation", in *Obesity in Europe* vol 88, pp. 371-376, Bjorntorp and Rossner, Eds., John Libbey Company Ltd., London, England (1989).

Dani et al., "Regulation of gene expression by insulin in adipose cells: opposite effects on adipsin and glycerophosphate dehydrogenase genes," *Mol. Cell. Endocri.*, 63:199-208 (1989).

Faust et al., "Diet-induced adipocyte number increase in adult rats: a new model of obesity," *Am. J. Physiol.*, 235:E279-E286 (1978).

Faust et al., "Surgical Removal of Adipose Tissue Alters Feeding Behavior and the Development of Obesity in Rats," *Science*, 197:393-396 (July 22, 1977).

Friedman et al., "Tackling a Weighty Problem," *Cell*, 69:217-220 (April 17, 1992).

Harris, "Role of set-point theory in regulation of body weight," *FASEB J.*, 4:3310-8 (1990).

Harris et al., "Body Composition of Lean and Obese Zucker Rats in Parabiosis," *Int. J. Obes.*, 11:275-283 (1987).

Hervey, "The Effects of Lesions in the Hypothalamus in Parabolic Rats," *J. Physiol.*, 145:336-352 (1959).

Ingalls et al., "Obese, A New Mutation in the House Mouse," *J. Hered.*, 41(12):317-8 (1950).

Johnson and Hirsch, "Cellularity of adipose depots in six strains of genetically obese mice," *J. Lipid Res.*, 13:2-11 (1972).

Keesey, in Association for Research in Nervous and Mental Disease, pp. 87-96, Stunkard and Stellar, eds., Raven Press, New York (1984).

Keesey et al., "the Regulation of Body Weight," *Ann. Rev. Psychol.*, 37:109-133 (1986).

Leibel et al., "Changes in Energy Expenditure Resulting From Altered Body Weight," *N. Engl. J. Med.*, 332(10):621-628 (March 9, 1995).

Leibel et al., "Genetic variation and nutrition in obesity: Approaches to the molecular genetics of obesity", in *World Review of Nutrition and Dietetics*, pp. 90-101, Simopoulos and Childs eds., S. Karger, Basel (1990).

Leibel et al., "Strategies for the Molecular Genetic Analysis of Obesity in Humans," *Crit. Rev. Food Sci. Nutr.*, 33(4/5):351-358 (1993).

Leiter et al., "The Influence of Genetic Background on the Expression of Mutations at the Diabetes Locus in the Mouse. V. Interaction between the db Gene and Hepatic Sex Steroid Sulfotransferases Correlates with Gender-Dependent Susceptibility to Hyperglycemia," *Endocrinology*, 124(2):912-922 (1989).

Moll et al., "The Genetic and Environmental Sources of Body Mass Index Variability: The Muscatine Ponderosity Family Study," *Am. J. Hum. Genet.*, 49:1243-1255 (1991).

Stunkard et al., "The Body-Mass Index of Twins Who Have Been Reared Apart," *N. Engl. J. Med.*, 322(21):1483-1487 (1990).

Trayhurn et al., "Acute cold-induced suppression of ob gene expression in white adipose tissue of mice: mediation by the sympathetic system," *Biochem J.*, 311:729-733 (1995).

Trayhurn et al., "Effects of fasting and refeeding on ob gene expression in white adipose tissue of lean and obese (ob/ob) mice," *FEBS Lett.*, 368:488-490 (1995).

Wasserman, "The Concept of the 'Fat Organ'" in Rodahl, Issekutz, fat as a tissue, pp. 22-92, McGraw Hill, New York (1964).

## **V. Gene Mapping (General)**

Tamura et al., "Assignment of the human PAX4 gene to chromosome band 7q32 by fluorescence in situ hybridization," *Cytogenet. Cell Genet.*, 66:132-134 (1994).

Bachmann et al., "Recalibrated Linkage Map of Escheria coli K-12," *Bacteriol. Rev.*, 40:116-167 (1976).

Bahary et al., "Microdissection and Microcloning of Mid-Chromosome 4: Genetic Mapping of 41 Microdissection Clones," *Genomics*, 16:113-122 (1993).

Bahary et al., "Microdissection of proximal mouse Chromosome 6: identification of RFLPs tightly linked to the ob mutation," *Mammalian Genome*, 4(9):511-515 (1993).

Bahary et al., "Molecular Genetic Linkage Maps of Mouse Chromosomes 4 and 6," *Genomics*, 11:33-47 (1991).

Bahary et al., "Molecular mapping of the mouse db mutation," *Proc. Nat. Acad. Sci. USA*, 87:8642-8646 (November 1990).

Bahary et al., "Molecular Mapping of Mouse Chromosomes 4 and 6: Use of a Flow-Sorted Robertsonian Chromosome," *Genomics*, 13:761-769 (1992).

Blank et al., "Mouse Chromosome 4," *Mammalian Genome*, 1:S51-S78 (1991).

Dausset et al., "The CEPH YAC Library," *Behring Inst. Mitt.*, 91:13-20 (1992).

Friedman et al., "Gen. Anal. of Comp. Disorders," *Ann. NY Acad. Sci.*, 630:100-115 (1991).

Friedman et al., "Molecular mapping of obesity genes," *Mam. Genome*, 1:130-144 (1991).

Green, "Physical mapping of human chromosomes: generation of chromosome-specific sequence-tagged sites", in *Methods in Molecular Genetics Vol. 1, Gene and Chromosome Analysis (Part A)*, pp. 192-210, Adolph ed., Academic Press, Inc., San Diego (1993).

Green and Green, "Sequence-tagged Site (STS) Content Mapping of Human Chromosomes: Theoretical Considerations and Early Experiences," *PCR Methods Applic.*, 1:77-90 (1991).

Green et al., "A Human Chromosome 7 Yeast Artificial Chromosome (YAC) Resource: Construction, Characterization, and Screening," *Genomics*, 25:170-183 (1995).

Green et al., "Integration of physical, genetic and cytogenetic maps of human chromosome 7: isolation and analysis of yeast artificial chromosome clones for 117 mapped genetic markers," *Hum. Mol. Genet.*, 3(3):489-501 (1994).

Green et al., "Systematic Generation of Sequence-Tagged Sites for Physical Mapping of Human Chromosomes: Application to the Mapping of Human Chromosome 7 Using Yeast Artificial Chromosomes," *Genomics*, 11:548-564 (1991).

Heng et al., "Fluorescence in situ hybridization mapping of the cystic fibrosis transmembrane conductance regulator (CFTR) gene 7q31.3," *Cytogenet Cell Genet.*, 62:108-109 (1993).

Tamura et al., "Assignment of the human PAX4 gene to chromosome band 7q32 by fluorescence in situ hybridization," *Cytogenet. Cell Genet.*, 66:132-134 (1994).

Truett et al., "Rat obesity gene fatty (fa) maps to chromosome 5: Evidence for homology with the mouse gene diabetes (db)," *Proc. Natl. Acad. Sci. USA*, 88:7806-7809 (September 1991).

Walther et al., "Pax: A Murine Multigene Family of Paired Box-Containing Genes," *Genomics*, 11:424-434 (1991).

## **VI. Pharmaceutical and Pharmacological Methods and Materials, Drug Delivery**

U.S. Patent No. 4,925,673 issued May 15, 1990; Steiner et al., "Delivery Systems for Pharmacological Agents Encapsulated with Protenoids"

U.S. Patent No. 4,946,778 issued August 7, 1990; Ladner et al., "Single Polypeptide Chain Binding Molecules"

U.S. Patent No. 5,013,556 issued May 7, 1991; Woodle et al., "Liposomes eith Enhanced Circulation Time"

U.S. Patent No. 5,284,656 issued February 8, 1994; Platz et al., "Pulmonary Administration of Granulocyte Colony Stimulating Factor"

Adjei et al., "Pulmonary Delivery of Peptide Drugs: Effect of Particle Size on Bioavailability of Leuprolide Acetate in Healthy Male Volunteers," *Pharm. Res.*, 7(6):565-569 (1990).

Baura et al., "Saturable Transport of Insulin from Plasma into the Central Nervous System of Dogs In Vivo," *J. Clin. Invest.*, 92:1824-1830 (October 1993).

Buchwald et al., "Long-term, continuous intravenous heparin administration by an implantable infusion pump in ambulatory patients with recurrent venous thrombosis," *Surgery*, 88:507-516 (October 1980).

Debs et al., "Lung-Specific Delivery of Cytokines Induces Sustained Pulmonary and Systemic Immunomodulation in Rats," *J. Immunol.*, 140(10):3482-3488 (May 15, 1988).

During et al., "Controlled Release of Dopamine from a Polymeric Brain Implant: In Vivo Characterization," *Ann. Neurol.*, 25:351 (1989).

Goodson, in *Medical Applications of Controlled Release*, vol. 2, pp. 115-138 (1984).

Howard et al., "Intracerebral drug delivery in rats with lesion-induced memory deficits," *J. Neurosurg.*, 71:105-112 (1989).

Hubbard et al., "Anti-Neutrophil-Elastase Defenses of the Lower Respiratory Tract in  $\alpha$ -1-Antitrypsin Deficiency Directly Augmented with an Aerosol of  $\alpha$ -1-Antitrypsin," *Annals of Internal Medicine*, 3(3):206-212 (1989).

Langer and Peppas, "Chemical and Physical Structure of Polymers as Carriers for Controlled Release of Bioactive Agents: A Review," *J. Macromol. Sci. Rev. Macromol. Chem.*, 23(1):61-126 (1983).

Marshall, in *Modern Pharmaceutics*, Chapter 10, Banker and Rhodes ed., (1979).

Saudek et al., "A Preliminary Trial of the Programmable Implantable Medication System for Insulin Delivery," *N. Engl. J. Med.*, 321:574 (1989).

Sefton, "Implantable Pumps," *CRC Crit. Ref. Biomed. Eng.*, 14(3):201-240 (1987).

Smith et al., "Pulmonary Deposition and Clearance of Aerosolized Alpha-1-Proteinase Inhibitor Administered to Dogs and to Sheep," *J. Clin. Invest.*, 84:1145-1146 (October 1989).

Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, pp. 353-365, Lopez-Berestein and Fidler eds., Liss, New York (1989).

## **VII. Molecular Biological and Recombinant Methods and Therapies**

U.S. Patent No. 4,650,764 issued March 17, 1987; Temin et al., "Helper Cell"

U.S. Patent No. 4,816,567 issued March 28, 1989; Cabilly et al., "Recombinant Immunoglobulin Preparations"

U.S. Patent No. 4,980,289 issued December 25, 1990; Temin et al., "Promoter Deficient Retroviral Vector"

U.S. Patent No. 5,124,263 issued June 23, 1992; Temin et al., "Recombinant Resistant Retroviral Helper Cell and Products Produced Thereby"

U.S. Patent No. 5,399,346 March 21, 1995; Anderson et al., "Gene Therapy"

Albertsen et al., "Construction and characterization of a yeast artificial chromosome library containing seven haploid human genome equivalents," *Proc. Natl. Acad. Sci. USA*, 87:4256-4260 (June 1990).

Anand et al., "A 6.5 genome equivalent multi access YAC library: construction, characterization, screening and storage," *Nucl. Acids Res.*, 18(8):1951-1956 (1990).

Anand et al., "Construction of yeast artificial chromosome libraries with large inserts using fractionation by pulsed-field gel electrophoresis," *Nucl. Acids Res.*, 17(9):3425-3433 (1989).

Bachmann et al., "Recalibrated Linkage Map of Escheria coli K-12," *Bacteriol. Rev.*, 40:116-167 (1976).

Benton and Davis, "Screening  $\lambda$  gt Recombinant clones by Hybridization to Single Plaques in situ," *Science*, 196:180 (1977).

Cech, "Ribozymes and Their Medical Implications," *J. Am. Med. Assoc.*, 260(20):3030-3034 (November 25, 1988).

Cwirla et al., "Peptides on phage: A vast library of peptides for identifying ligands," *Proc. Natl. Acad. Sci. USA*, 87:6378-6382 (August 1990).

Dausset et al., "The CEPH YAC Library," *Behring Inst. Mitt.*, 91:13-20 (1992).

Edge, "Total synthesis of a human leukocyte interferon gene," *Nature*, 292:756 (1981).

Felgner et al., "Lipofection: A highly efficient, lipid-mediated DNA-transfection procedure," *Proc. Natl. Acad. Sci. USA*, 84:7413-7417 (November 1987).

Green, "Physical mapping of human chromosomes: generation of chromosome-specific sequence-tagged sites", in *Methods in Molecular Genetics Vol. 1, Gene and Chromosome Analysis (Part A)*, pp. 192-210, Adolph ed., Academic Press, Inc., San Diego (1993).

Green and Green, "Sequence-tagged Site (STS) Content Mapping of Human Chromosomes: Theoretical Considerations and Early Experiences," *PCR Methods Applic.*, 1:77-90 (1991).

Green and Olson, "Systematic screening of yeast artificial-chromosome libraries by use of the polymerase chain reaction," *Proc. Natl. Acad. Sci. USA*, 87:1213-1217 (February 1990).

Grunstein and Hogness, "Colony hybridization: A method for the isolation of cloned DNAs that contain a specific gene," *Proc. Natl. Acad. Sci. USA*, 72(10):3961 (October 1975).

Machy et al., "Gene transfer from targeted liposomes to specific lymphoid cells by electroporation," *Proc. Natl. Acad. Sci. USA*, 85:8027-8031 (November 1988).

Mann et al., "Construction of a Retrovirus Packaging Mutant and Its Use to Produce Helper-Free Defective Retrovirus," *Cell*, 33:153-159 (May 1983).

Marcus-Sekura, "Techniques for Using Antisense Oligodeoxyribonucleotides to Study Gene Expression," *Anal. Biochem.*, 172:289-295 (1988).

Samulski et al., "A Recombinant Plasmid from Which an Infectious Adeno-Associated Virus Genome Can Be Excised In Vitro and Its Use To Study Viral Replication," *J. Virol.*, 61(10):3096-3101 (October 1987).

Samulski et al., "Helper-Free Stocks of Recombinant Adeno-Associated Viruses: Normal Integration Does Not Require Viral Gene Expression," *J. Virol.*, 63(9):3822-3828 (1989).

Schaeren-Wiemers and Gerfin-Moser, "A single protocol to detect transcripts of various types and expression levels in neural tissue and cultured cells in situ hybridization using digoxigenin-labelled cRNA probes," *Histochemistry*, 100:431-440 (1993).

Stratford-Perricaudet et al., "Widespread Long-term Gene Transfer to Mouse Skeletal Muscles and Heart," *J. Clin. Invest.*, 90:626-630 (August 1992).

Studier et al., "Use of T7 RNA Polymerase to Direct Expression of Cloned Genes," *Meth. Enzymology*, 185:80-89 (1990).

Takeda et al., "Construction of chimeric processed immunoglobulin genes containing mouse variable and human constant region sequences," *Nature*, 314:452-454 (1985).

Wilson et al., "Hepatocyte-directed Gene Transfer In Vivo Leads to Transient Improvement of Hypercholesterolemia in Low Density Lipoprotein Receptor-deficient Rabbits," *J. Biol. Chem.*, 267(2):963-967 (January 15, 1992).

Wu and Wu, "Receptor-mediated Gene Delivery and Expression in Vivo," *J. Biol. Chem.*, 263(29):14621-14624 (October 15, 1988).

WO 90/14092 11/29/90 PCT "Single-Strand Site-Directed Modification of Mammalian Genes In Vivo"

WO 91/06666 05/16/91 PCT "Production of Proteins Using Homologous Recombination"

WO 91/09955 07/11/91 PCT "Endogenous Gene Expression Modification with Regulatory

Element"

WO 95/07358 03/16/95 PCT "Efficient Gene Transfer into Primary Lymphocytes"

### **VIII. Modification of Proteins**

U.S. Patent No. 4,179,337 issued December 18, 1979; Davis et al., "Non-Immunogenic Polypeptides"

Francis, "Protein modification and fusion proteins," Focus on Growth Factors, 3:4-10 (1992).

Malik et al., "Polyethylene Glycol (PEG)-modified Granulocyte-Macrophage Colony-stimulating Factor (GM-CSF) with Conserved Biological Activity," Exp. Hematol., 20:1028-1035 (1992).

Newmark et al., "Preparation and Properties of Adducts of Streptokinase and Streptokinase-Plamin Complex with Polyethylene Glycol and Pluronic Polyol F38," J. Appl. Biochem., 4:185-189 (1982).

CA 2,012,311 09/16/90 Canada "New Protein-Polycation-Conjugate"

EP 0 401 384 B1 03/13/96 EPO "Chemically Modified Granulocyte Colony Stimulating Factor"

### **IX. Immunological Materials and Methods**

U.S. Patent No. 4,341,761 issued July 27, 1982; Ganfield et al., "Antibodies to Immunogenic Peptides and Their Use to Purify Human Fibroblase Interferon"

U.S. Patent No. 4,342,566 issued August 3, 1982; Theofilopoulos et al., "Solid Phase ANTI-C3 Assay for Detection of Immune Complexes"

U.S. Patent No. 4,399,121 issued August 16, 1983; Albarella et al., "Iodothyronine Immunogenes and Antibodies"

U.S. Patent No. 4,427,783 issued January 24, 1984; Newman et al., "Immunoassay of Thymosin"

U.S. Patent No. 4,444,887 issued April 24, 1984; Hoffmann, "Process for Making Human Antibody Producing B-Lymphocytes"

U.S. Patent No. 4,451,570 issued May 29, 1984; Royston et al., "Immunoglobulin-Secreting Human Hybridomas From a Cultured Human Lymphoblastoid Cell Line"

U.S. Patent No. 4,466,917 issued August 21, 1984; Nussenzweig et al., "Malaria Vaccine"

U.S. Patent No. 4,472,500 issued September 18, 1984; Milstein et al., "Rat Myeloma Cell Lines"

U.S. Patent No. 4,491,632 issued January 1, 1985; Wands et al., "Process for Producing Antibodies to Hepatitis Virus and Cell Lines Therefor"

U.S. Patent No. 4,493,890 issued January 15, 1985; Morris, "Activated Apoglucose Oxidase and Its Use in Specific Binding Assays"

U.S. Patent No. 4,816,567 issued March 28, 1989; Cabilly et al., "Recombinant Immunoglobulin Preparations"

U.S. Patent No. 4,925,673 issued May 15, 1990; Steiner et al., "Delivery Systems for Pharmacological Agents Encapsulated with Proteinoids"

U.S. Patent No. 4,946,778 issued August 7, 1990; Ladner et al., "Single Polypeptide Chain

## Binding Molecules"

Cole et al., in *Monoclonal Antibodies and Cancer Therapy*, pp. 77-96, Alan R. Liss, Inc., (1985).

Cote et al., "Generation of human monoclonal antibodies reactive with cellular antigens," *Proc. Natl. Acad. Sci. USA*, 80:2026-2030 (April 1983).

Geysen et al., "A Priori Delineation of a Peptide Which Mimics a Discontinuous Antigenic Determinant," *Molecular Immunology*, 23(7):709-715 (1986).

Geysen et al., "Strategies for epitope analysis using peptide synthesis," *J. Immunologic Method*, 102:259-274 (1987).

Hopp and Woods, "Prediction of protein antigenic determinants from amino acid sequences," *Proc. Natl. Acad. Sci. USA*, 78(6):3824-3828 (June 1981).

Kohler and Milstein, "Continuous cultures of fused cells secreting antibody of predefined specificity," *Nature*, 256:495-497 (August 7, 1975).

Kozbor and Roder, "The production of monoclonal antibodies from human lymphocytes," *Immunology Today*, 4(3):72-79 (1983).

Neuberger et al., "Recombinant antibodies possessing novel effector functions," *Nature*, 312:604-608 (December 1984).

Takeda et al., "Construction of chimeric processed immunoglobulin genes containing mouse variable and human constant region sequences," *Nature*, 314:452-454 (1985).

## X. Analytical Methods

U. S. Patent No. RE 31,006 issued August 3, 1982; Schuurs et al., "Process for the Demonstration and Determination of Reaction Components Having Specific Binding Affinity for Each Other"

U.S. Patent No. 3,650,090 issued March 21, 1972; Temple et al., "Analysis of Gaseous Mixtures"

U.S. Patent No. 3,654,090 issued April 4, 1972; Wilhemus et al., "Method for the Determination of Antigens and Antibodies"

U.S. Patent No. 3,850,752 issued November 26, 1974; Schuurs et al., "Process for the Demonstration and Determination of Low Molecular Compounds and of Proteins Capable of Binding These Compounds Specifically"

U.S. Patent No. 4,016,043 issued April 5, 1977; Schuurs et al., "Enzymatic Immunological Method for the Determination of Antigens and Antibodies"

U.S. Patent No. 4,342,566 issued August 3, 1982; Theofilopoulos et al., "Solid Phase ANTI-C3 Assay for Detection of Immune Complexes"

Bax and Davis, "MLEV-17-Based Two-Dimensional Homonuclear Magnetization Transfer Spectroscopy," *J. Magn. Reson.*, 65:355-360 (1985).

Chou and Fasman, "Prediction of Protein Conformation," *Biochem.*, 13(2):222-245 (1974).

Cohen et al., "Probing the solution structure of the DNA-binding protein Max by a combination of proteolysis and mass spectrometry," *Protein Science*, 4:1088 (1995).

Madej et al., "Threading analysis suggests that the obese gene product may be a helical cytokine," *FEBS Lett.*, 373:13-18 (1995).

Marion and Wuthrich, "Application of Phase Sensitive Two-Dimensional Correlated Spectroscopy (COSY) for Measurements of  $^1\text{H}$ - $^1\text{H}$  Srin-Spin Coupling Constants in Proteins," *Biochem. Biophys. Res. Comm.*, 113(3):967-974 (June 29, 1983).

Pardridge, "Receptor-Mediated Peptide Transport through the Blood-Brain Barrier," *Endocrine Reviews*, 7(3):314-330 (1986).

von Heijne, "A new method for predicting signal sequence cleavage sites," *Nucl. Acids Res.*, 14(11):4683-4690 (1986).

## **XI. Synthetic Methods**

U.S. Patent No. 4,631,211 issued December 23, 1996; Houghten, "Means For Sequential Solid Phase Organic Synthesis and Methods Using the Same"

U.S. Patent No. 5,010,175 issued April 23, 1991; Rutter et al., "General Method for Producing and Selecting Peptides with Specific Properties"

Edge, "Total synthesis of a human leukocyte interferon gene," *Nature*, 292:756 (August 20, 1981).

Furka, "General method for rapid synthesis of multicomponent peptide mixtures," *Int. J. Peptide Protein Res.*, 37:487-493 (1991).

Geysen et al., "Strategies for epitope analysis using peptide synthesis," *J. Immunologic Method*, 102:259-274 (1987).

Needels et al., "Generation and screening of an oligonucleotide-encoded synthetic peptide library," *Proc. Natl. Acad. Sci. USA*, 90:10700-10704 (November 1993).

## **XII. Receptors/Ligands**

U.S. Patent No. 4,981,784 issued January 1, 1991; Evans et al., "Retinoic Acid Receptor Method"

Cwirla et al., "Peptides on phage: A vast library of peptides for identifying ligands," *Proc. Natl. Acad. Sci. USA*, 87:6378-6382 (August 1990).

Wu and Wu, "Receptor-mediated Gene Delivery and Expression in Vivo," *J. Biol. Chem.*, 263(29):14621-14624 (October 15, 1988).

WO 88/03168 05/05/88 PCT "Hormone Receptor Compositions and Methods"

## **XIII. Miscellaneous**

Braquet et al., "Effect of Endothelin-1 on Blood Pressure and Bronchopulmonary System of the Guinea Pig," *Journal of Cardiovascular Pharmacology*, 13(suppl. 5):S143-S146 (1989).

Dickie and Lane, *Mouse News Lett.*, 17:52 (1957).

Ellman, "Tissue Sulfhydryl Groups," *Arch. Biochem. Biophys.*, 82:70-77 (1959).

Engstrom, "The Arrangement of the Protein Molecules in Nuclear-Polyhedrosis Inclusions," *Biochem. Exp. Biol.*, 11:7-13 (1974).

Green et al., "The Role of Antisense RNA in Gene Regulation," *Annu. Rev. Biochem.*, 55:569-597 (1986).

Hambor et al., "Functional Consequences of Anti-Sense RNA-Mediated Inhibition of CD8 Surface Expression in a Human T Cell Clone," *J. Exp. Med.*, 168:1237-1245 (October 1988).

Harris, "Epidemiological Correlates of NIDDM in Hispanics, Whites, and Blacks in the U.S. Population," *Diabetes Care*, 14(7):639-648 (July 1991).

Harris et al., "Prevalence of Diabetes and Impaired Glucose Tolerance and Plasma Glucose Levels in U.S. Population Aged 20-74 Yr," Diabetes, 36:523-534 (April 1987).

Hood et al., in Immunology, p. 384, Second Ed., Benjamin/Cummings, Menlo Park, California (1984).

Hopp and Woods, "Prediction of protein antigenic determinants from amino acid sequences," Proc. Natl. Acad. Sci. USA, 78(6):3824-3828 (June 1981).

Izant and Weintraub, "Inhibition of Thymidine Kinase Gene Expression by Anti-Sense RNA: A Molecular Approach to Genetic Analysis," Cell, 36:1007-1015 (April 1984).

Jacobsson et al., "Mitochondrial Uncoupling Protein from Mouse Brown Fat," J. Biol. Chem., 260(30):16250-16254 (December 25, 1985).

Kaplitt et al., "Expression of a Functional Foreign Gene in Adult Mammalian Brain following In Vivo Transfer via a Herpes Simplex Virus Type 1 Defective Viral Vector," Molec. Cell. Neurosci., 2:320-330 (1991).

Kimura et al., "Probable precursors of [Leu]enkephalin and [Met]enkephalin in adrenal medula: Peptides of 3-5 kilodaltons," Proc. Natl. Acad. Sci. USA, 77(3):1681-1685 (March 1980).

Madej et al., "Threading analysis suggests that the obese gene product may be a helical cytokine," FEBS Lett., 373:13-18 (1995).

Pardridge, "Receptor-Mediated Peptide Transport through the Blood-Brain Barrier," Endocrine Reviews, 7(3):314-330 (1986).

Richardson et al., "Expression of Transforming Growth Factor- $\beta$  (TGF- $\beta$ 1) and Insulin-Like Growth Factor II (IGF-II) Messenger RNA in the Developing Subcutaneous Tissue (SQ) of the Fetal Pig," Growth, Development & Aging, 56:149-157 (1992).

Smith and Johnson, "Single-step purification of polypeptides expressed in Escherichia coli as fusions with glutathione S-transferase," Gene, 67:31-40 (1988).

WO 90/03431 04/05/90 PCT "Mixed Feed Recombinant Yeast Fermentation"

WO 90/10697 09/20/90 PCT "Production of Epidermal Growth Factor in Methylophilic Yeast Cells"

WO 92/00252 01/09/92 PCT "Fluidized Calcining Process"

No fee is believed due for the filing of this statement inasmuch as it is being filed before the mailing of the first official action on the merits. However, should the Patent and Trademark Office determine otherwise, authorization is hereby given to charge Deposit Account No. 11-1153 for this filing.

Respectfully submitted,



David A. Jackson  
Attorney for Applicants  
Registration No. 26,742

KLAUBER & JACKSON  
411 Hackensack Avenue  
Hackensack, New Jersey 07601  
(201) 487-5800  
E-mail: kjiplaw@camba.com or 6261210@mcimail.com